Law and the Public's Health

INCREASING TRANSPARENCY AT THE FDA: THE IMPACT OF THE FDA AMENDMENTS ACT OF 2007

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On September 27, 2007, the Food and Drug Administration Amendments Act (FDAAA)¹ was signed into law. Containing 11 titles, the legislation addresses a wide variety of legal and scientific issues facing the FDA currently and in the future. At the same time, the primary purpose of the law, and the speed with which it moved through the 110th Congress, was to reauthorize major mechanisms by which FDA activities are financed, with new provisions on product safety. In addition, the legislation addresses the manner in which the FDA carries out its core agency functions of expert consultation, scientific publication, and diffusion of scientific information.

This installment of *Law and the Public's Health* examines those provisions of the Act that focus on the approval decision-making process and financial conflicts of interest (COIs), increased access to data flowing from clinical studies, and publication of scientific research by FDA scientists.

BACKGROUND

Rigor, transparency, and impartiality are the hallmarks of a high-performing public health system. In no context are these considerations more important than at the FDA. In U.S. law, primary authority for assuring drug safety and for promoting the best evidence in matters of food and drugs lies with the federal government; since enactment of the original Federal Food, Drug and Cosmetic Act of 1938, the power and duty to assure the safety of prescription drugs has been carried out by the FDA.

Over the past several years, concerns have arisen regarding various aspects of FDA performance. Concerns have focused on actual and apparent financial COIs, restraints on scientific publication, and access to timely and complete data from clinical trials related to the drug approval process. In recent years, the volume of criticism has significantly elevated; several FDA scientists (some of whom have received formal designations as whistleblowers) have come forward.

Additional evidence has emerged through reports issued from national organizations; academic, scientific, and medical experts; and leading journals.²⁻⁶ Reports issued by the Institute of Medicine² on the drug safety system and the FDA Science Board³ on the state of science at the FDA also identified critical problems in the scientific infrastructure and culture of the agency. These various reports and studies focused extensively on these major issues.

FDA advisory committees and financial COIs

FDA drug approval rests in part on a decision-making process in which the agency may be informed by a formal committee advisory structure; the impartiality and rigor of these committees is paramount to the quality and reliability of FDA review. However, questions about the objectivity and scientific scrutiny of FDA advisory committees have been raised in several analyses and reports, with specific concerns about the impact of financial COIs.³⁻⁵

FDA advisory committees are used when the agency is seeking external expert advice on either specific products or a broader topic, and members include scientists, clinicians, consumers, and patient and industry representatives. Members discuss questions posed by the FDA and usually vote on recommendations to the agency. Financial conflicts can include stocks, employment, consulting, research grants and contracts, speaking or writing fees, or serving as an expert witness.⁷ The FDA has had the authority to grant waivers to allow participation of members with financial COIs, and the majority of advisory committee meetings have had at least one member with a COI, with more than 20% of meetings having more than half of the members with COIs.⁴ A recent FDA report sampled committees and found that 26% of members were granted waivers for COIs.⁸

Publication by FDA scientists

A 2006 survey by the Union of Concerned Scientists reported the views of FDA scientists regarding candor at the FDA. Thirty-six percent of the nearly 1,000 respondents felt that they could not express concerns about public health within the agency, and 40% felt that they could not express concerns outside the agency without fear of retaliation.⁶ In addition, recent highly publicized drug safety concerns have shown some of the challenges involved in acquiring FDA approval

for the publication of safety analyses. Dr. David Graham, an FDA scientist who identified an association between a COX-2 inhibitor and increased heart attack risk, experienced difficulty attaining authorization to publish the results of his study. He noted in his 2004 Congressional testimony, "Senior managers in the Office of Drug Safety have not granted clearance for [the manuscript's] publication, even though it was accepted for publication in a very prestigious journal after rigorous peer review by that journal."⁹ The Center for Drug Evaluation and Research within the FDA has a policy to allow for publication,¹⁰ however it does not place time limits on review by supervisors.

Clinical trials results database

For several years, commentators and experts have called for improved access to the results of studies funded by the medical product industry. Recently, drug safety concerns for products such as rosiglitazone¹¹ and antidepressants¹² demonstrated the extent to which access to unpublished data can yield important information on the safety and efficacy of products.

The 2007 legislation

The 2007 amendments reauthorize the major user-fee systems for drugs, biologics, and medical devices, which provide a significant portion of the FDA budget.¹³ However, accompanying these basic provisions are, among other matters, new provisions that address drug and device safety, COIs, expanded access to clinical trial databases, and the establishment of policies on scientific publications by FDA employees.

COIs. The new law now limits waivers that can be issued for COIs on the part of FDA advisory committee members at the current level and requires a reduction of 5% per year over the next five years. The legislation also directs the FDA to develop and implement strategies for better recruitment of non-conflicted individuals from "universities, colleges, other academic research centers, professional and medical societies, and patient and consumer groups."¹⁴

Concurrently, the FDA has issued new draft guidelines on financial COIs. In March 2007, the agency proposed a more stringent policy that would generally prohibit waivers for conflicts greater than \$50,000. For any financial conflict less than \$50,000, a waiver could be granted, but only to participate as a non-voting member.¹⁵ In later months, the FDA issued further draft guidelines calling for early disclosure of conflicts and waivers granted¹⁶ and proposing a change to the voting procedure from sequential voting to simultaneous voting.¹⁷ Studies have examined the impact of sequential

votes being influenced by previous votes, and the FDA states in its guidance, "This potential risk may be aggravated in the advisory committee setting, where votes are often conducted in full view of a passionate public and participatory audience," and that comments by a committee member "could inappropriately affect the deliberations of those who have not yet voted."¹⁷

Scientific publication. The FDAAA establishes parameters to ensure timely review of any proposed scientific article by FDA employees. The statute directs the Secretary to make publicly available clear written policies for the "timely submission, review, clearance and disclaimer requirements for articles,"¹⁴ and supervisors must make a determination within 30 days after the article is submitted by the author. The policy must allow FDA scientists to publish even without approval of the agency, with an appropriate disclaimer.

Access to clinical data. The FDAAA includes new provisions expanding the clinical trials database at the National Institutes of Health (NIH) to enhance patient enrollment, provide access to results, and offer the ability to track the progress of clinical trials, other than Phase I studies, regulated by the FDA.¹⁸ The database will include descriptive information about the trial (including expected completion dates, and primary and secondary outcomes) and this will be publicly available.

Within one year of enactment, the database will include results of studies conducted on approved drugs or cleared medical devices, and must include information on the demographics of the patients studied, the primary and secondary outcome results, an identified contact for further scientific information, and disclosure of any agreements between the study sponsor and the investigator that might restrict the investigator from speaking about or publishing the results after completion of the trial. Within three years of enactment, the FDA is to issue further regulations regarding submission of results, particularly on the development of nontechnical summaries that can be understood by patients, and of technical summaries that are not misleading or promotional. Within 18 months of enactment, a mechanism for reporting of serious adverse events is to be added to the database.

CONCLUSIONS AND IMPLICATIONS

Rigor, evidence, and transparency are fundamental to public health. Increasing transparency is one way to foster scientific and regulatory independence at the FDA. The 2007 legislation, with its provisions for conflicts, transparency, and scientific freedom, may

have begun to restore confidence in and capability of the FDA.

The impact of changes in the allowable financial COI waivers for FDA advisory committee members may be difficult to measure, as indeed direct effects of financial ties are not obvious and effects are often based on group dynamics.³⁻⁵ At the same time, it should not be difficult to attract a broader group of outside experts who do not have financial COIs to serve on the advisory committees. The recent report commissioned by the FDA notes that qualified experts are available, but it will require additional resources and efforts to identify them and stimulate their participation in an advisory committee.³ FDAAA in fact calls for such additional effort. Currently, there are fewer than 500 advisory committee and device panel members needed to fill the existing 30 committees and 18 panels.⁷ At the same time, there are more than 120,000 medical school faculty,¹⁹ more than 4,000 pharmacy faculty,²⁰ and approximately 7,500 public health faculty in the U.S.²¹ Many of these are publicly funded (although some will also have industry-funded research) as the NIH awarded more than 45,000 research grants in fiscal year 2006.²² These numbers reveal a very large pool of potential advisory committee members, and with enhanced resources and outreach, the goal of reducing or eliminating financial COIs is quite feasible.

Scientific freedom for government employees is a more complex matter. The concept of scientific freedom in academic settings encompasses the right to publish findings. The guidelines of the University of California, for example, assert that research is a component and outcome of an academic environment characterized by the free and open exchange of ideas: "Freedom to publish is fundamental to the University and is a major criterion of the appropriateness of a research project."²³ Government scientists, on the other hand, do not generally have equal freedoms, given the balance that must be struck among their roles as researchers, regulators, applied scientists, and government employees with regulatory responsibilities. Government research may be subjected to several levels of review, sometimes involving political appointees, before submission for publication. How to achieve this balance is the policy challenge.

The FDAAA assures FDA scientists the right to publish with timely review, and the ability to publish without supervisory approval and with appropriate disclaimers. This standard moves toward a more reasonable approach for government scientists, while also assuring greater public access to scientific opinions and conclusions of FDA scientists.

Finally, access to the results of FDA-regulated clinical

studies will allow outside scientists to evaluate data from studies completed but not necessarily published on products approved by the FDA. The ClinicalTrials.gov database was originally created to allow increased patient access to enrollment in efficacy studies for serious and life-threatening conditions. The medical and scientific communities have since called for access to results from postmarket studies or studies on new indications. This will require a large expansion of the existing clinical trials registry (ClinicalTrials.gov) and will also require the FDA to develop methods and regulations on data reporting and the creation of nontechnical and technical summaries.

With the increased involvement of universities in commercial enterprises and collaborations, many universities require that faculty members who enter into contractual agreements for sponsored research retain full rights to publish and otherwise disclose information developed in the research. The FDAAA further strengthens transparency by requiring disclosure of any restrictions on public presentation or publication of results of studies funded by industry. This requirement allows for public evaluation of both the data and the research environment, potentially transforming some of the current research on new medical products.

The FDAAA begins to address many of the challenges facing the FDA. The provisions reviewed in this article illustrate a subset of the many parts of the legislation, which is authorized for the next five years. Ultimately, the impact depends on the implementation of these provisions, the resources available to the FDA to fully carry them out, and the will of FDA leadership.

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